The Clinicopathological Factors Associated with Multicentricity in Papillary Thyroid Cancer

Papiller Tiroid Kanserinde Multisentrisite ile İlişkili Klinikopatolojik Faktörler

Multicentricity in Papillary Thyroid Cancer

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Özet

Amaç: Multisentrisite papiller tiroid kanserinin sık bir özelliğidir ve genellikle ileri evre, bölgesel ve uzak metastaz riskinde artış ile ilişkilidir. Bu çalışmada, papiller tiroid kanserinde multisentrisite ile ilişkili klinikopatolojik faktörlerin belirlenmesini amaçladık. Gereç ve Yöntem: Papiller tiroid kanseri olan yüz otuz hasta bu retrospektif çalışmaya dahil edildi. Multisentrisiteyi etkileyen klinik ve histopatolojik faktörler araştırıldı. Bulgular: Yaş ortalaması 43.03 olan 130 hastaya (101,% 77.7 kadın ve 29 erkek % 22.3) total tiroidektomi ve/veya santral/lateral boyun diseksiyonu uygulandı. Papiller tiroid kanseri tanısı her olguda histopatoloji ile kesinleştirildi. Multisentrisite ve bilateralite sırasıyla 54 (% 41.5) ve 16 (% 12.3) hastada saptandı. Tümör boyutu (p = 0.046) ve perinöral invazyon (p = 0.020) multisentrik kanserli hastalar ile soliter kanserli hastalar arasında anlamlı derecede farklı idi. Tartışma: Bu çalışmadan elde edilen bulgulara göre, tümör boyutu ve perinöral invazyon papiller tiroid kanserinde multisentrisiteyi etkileyen faktörlerdir. Ancak, büyük ölçekli, çok merkezli klinik ve genetik çalışmalar bu kanserlerin multisentrisitesini etkileyen faktörleri net olarak belirlemek için gereklidir.

Anahtar Kelimeler

Bilateralite; Multisentrisite; Papiller Tiroid Kanser

Abstract

Aim: Multicentricity is a frequent feature of papillary thyroid cancer, and is generally associated with advanced stage, increased risk of regional and distant metastasis. In this study, we aimed to determine the associated clinicopathological factors on multicentricity in papillary thyroid cancer. Material and Method: One hundred and thirty patients with papillary thyroid cancer were included in this retrospective study. The affecting clinical and histopathological factors on multicentricity were investigated. Results: Total thyroidectomy with or without central/lateral neck dissection was performed in 130 patients (101, 77.7% were female and 29, 22.3% were male) with a mean age of 43.03 years. The diagnosis of papillary thyroid cancer was confirmed by final histopathology in all cases. Multicentricity and bilaterality were detected in 54 (41.5%) and 16 (12.3%) patients, respectively. Tumor size (p= 0.046) and perineural invasion (p= 0.020) were significantly different between the patients with multicentric cancer and those with solitary cancer. Discussion: According to the findings obtained from this study, tumor size and perineural invasion were the affecting factors on multicentricity in papillary thyroid cancer. However, large-scale, multicenter clinical and genetic studies are needed to clearly determine the affecting factors on multicentricity of these cancers.

Keywords

Bilaterality; Multicentricity; Papillary Thyroid Cancer

DOI: 10.4328/JCAM.4256 Received: 31.12.2015 Accepted: 27.01.2016 Printed: 01.07.2016 J Clin Anal Med 2016;7(4): 479-82
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Introduction

Thyroid cancer is the most frequent endocrine malignancy with an increasing incidence in recent decades due to advanced diagnostic tools such as fine needle aspiration biopsy [1]. Papillary thyroid carcinoma (PTC) is the most common thyroid malignancy, accounting for 70% to 80% of all thyroid cancers [2]. These cancers originate in the follicular cells of the thyroid gland and generally have a good prognosis if properly treated. However, some conditions such as extrathyroidal invasion, lymph node involvement, advanced stage, distant metastasis, and inadequate surgical therapy are related to high risk of recurrence and poor prognosis. In addition, multifocality or multicentricity is a frequent feature of these tumors, and is generally associated with advanced stage, increased risk of lymph node involvement, and the presence of distant metastasis, in comparison to solitary PTC [3, 4]. In the literature, there are numerous studies comparing multifocal/bilateral and solitary PTCs; however, the risk factors affecting multifocality/multicentricity or bilaterality are not clear. In this study, we aimed to determine the possible clinicopathological factors affecting multicentricity and bilaterality in PTC.

Material and Method

Patients and study design

Between 2010 and 2015, a total of 130 patients with PTC underwent thyroid surgery at Turgut Ozal University Hospital in Ankara, Turkey. All operations were performed by the same surgical team. The diagnosis of PTC was confirmed at the final histopathological examination in all patients. Patients' demographic data such as age and gender, and clinicopathological features of the tumors including tumor size, stage, the number of nodules, presence of Hashimato thyroiditis and calcifications, extrathyroidal extension, and vascular, lymphatic, and perineural invasions, were recorded. The tumors were classified as multicentric/bilateral or solitary PTC. The surgical type and recurrences were also noted. The primary endpoint of the study was the association between demographic/clinicopathological factors and multicentricity/bilaterality of PTC.

Statistical analysis

The Statistical Package for the Social Science (SPSS 21.0 software, IL-Chicago- USA) was used for data analyses. Descriptive analysis was done for patient demographics and clinicopathological features. The results were presented as mean ± SD/percentages for continuous variables, and number/percentage for categorical variables. Mann Whitney U test, Fisher's exact test, and chi-square test were used for investigating the differences between the groups and subgroups. Significance level was accepted as $p < 0.05$.

Results

A total of 130 patients with a mean age of 43.03 were included in the study. Of these patients, 101 (77.7%) were female and 29 (22.3%) were male. All patients underwent total thyroidectomy with or without central/lateral neck dissection for a diagnosis of PTC. The mean diameter of the tumors was 15.8 mm, and the majority of patients (n= 109, 83.8.%) had early stages (stage 1 or 2) of the tumor. All patient demographics and the clinicopathological characteristics of the tumors are presented in Table 1.

Table 1. Demographic data and clinicopathological characteristics of the patients (n= 130)

Characteristics	n (%)
Age (y)	43.03±14.2 y (18-78)
Gender	
male	101 (77.7%)
female	29 (22.3%)
Number of nodules	
One	33 (25.4%)
Two	15 (11.5%)
Three or more	82 (63.1%)
Tumor size (mm)	15.81±10.09 mm (3-45 mm)
Stage	
Stage 1	106 (81.5%)
Stage 2	3 (2.3%)
Stage 3	17 (13.1%)
Stage 4	4 (3.1%)
Lymphatic invasion	12 (9.2%)
Vascular invasion	5 (3.8%)
Perineural invasion	7 (5.4%)
Extrathyroidal invasion	41 (31.5%)
Hashimato thyroiditis	41 (31.5%)
Calcification	72 (55.4%)
Multicentricity	54 (41.5%)
Bilaterality	16 (12.3%)
Duration of follow-up (d)	34,68±21.57 d (3-90)
Recurrence	12 (9.2%)

Age, tumor size, and duration of follow-up were presented as mean±SD (range); other variables were presented as number (percentage). y: year, mm: milimeter, d: day

More than half of the patients (n= 76, 58.5%) had solitary PTC. Multicentricity and bilaterality were detected in 54 (41.5%) and 16 (12.3%) patients, respectively, at the final pathology. The differences in all demographic, clinical, and pathological characteristics between patients with solitary cancer and those with multicentric/bilateral cancers were statistically assessed. Tumor size was significantly found to be larger in patients who had multicentric PTC than the patients with solitary cancer (p= 0.046). There was also significant difference in perineural invasion between multicentric and solitary cancers (p= 0.020).

Four patients had distant metastasis (all were micrometastasis located in the lung). All recurrences were in the form of locoregional recurrence, and reoperation was performed for these cases. Lateral neck dissection was also performed when there was a recurrence in cervical lymph nodes. Although recurrence rate was higher in patients with multicentric tumor than in those with solitary tumor, this was not statistically significant (p= 0.371). No association was found between multicentric/bilateral tumors and solitary tumors in terms of other clinicopathological parameters. All the statistical analyses comparing these two groups are presented in Table 2.

Discussion

Although there is not a certain definition of multifocality and

Table 2. The comparison of clinical and pathological findings between multicentric and solitary PTCs

Parameters	Solitary PTC (n= 76)	Multicentric PTC (n= 54)	P value
Age (y)	43.28 y (18-78)	42.69 y (18-66)	0.930
Gender			0.579
male	17 (22.3%)	12 (22.2%)	
female	59 (77.7%)	42 (77.8%)	
Number of nodules			0.088
One	23 (30.2%)	10 (18.5%)	
Two	11(14.7%)	4 (7.4%)	
Three or more	42 (55.2%)	40 (74%)	
Tumor size (mm)	14.3 mm (3-40)	17.8 mm (5-45)	0.046
Stage			0.745
Stage 1	62 (81.5%)	44 (81.4%)	
Stage 2	1 (1.3%)	2 (3.7%)	
Stage 3	10 (13.1%)	7 (12.9%)	
Stage 4	3 (3.9%)	1 (1.8%)	
Lymphatic invasion	6 (7.9%)	6 (11.1%)	0.371
Vascular invasion	2 (2.6%)	3 (5.6%)	0.342
Perineural invasion	1 (1.3%)	6 (11.1%)	0.020
Extrathyroidal invasion	27 (35.5%)	14 (25.9%)	0.166
Hashimato thyroiditis	22 (28.9%)	19 (25.1%)	0.286
Calcification	40 (52.6%)	32 (59.2%)	0.285
Recurrence	6 (7.9%)	6 (11.1%)	0.371

Age and tumor size were presented as mean±SD (range); other variables were presented as number (percentage). y: year, mm: milimeter

multicentricity in thyroid cancer, multicentricity indicates more than one tumor focus in one or two thyroid lobes while multifocality is generally defined as more than one tumor focus in only one thyroid lobe [5]. Therefore, the term of multicentricity includes both multifocal and bilateral cancers. In this study, we primarily investigated the associated factors on multicentricity in PTC. Bilateral cancers, as a distinct subgroup of multicentric tumors, were also examined in terms of associated clinicopathological factors.

Multicentricity is a common feature of PTC, with an incidence of up to 40% [6]. Similarly, multicentricity was found in 41.5% of our study population. Of these patients, 12.3% also had a tumor focus in the contralateral lobe. It is well known that some clinical factors such as male gender, age above 45 years, aggresssive histologic subtypes including tall cell, columnar cell, and diffuse sclerosing variants of PTC, tumor size greater than 4 cm, presence of extrathyroidal extension, and regional or distant metastasis are associated with poor outcomes in PTC. In addition to all these factors, multicentricity is also considered a negative prognostic parameter of PTC. In many studies, multicentricity was found to be an independent risk factor for regional metastatic dissemination [6-8]. In contrast, Zhang et al. [9] showed that extrathyroidal extension and maximum tumor diameter greater than 1 cm, but not multifocality or multicentricity, were the independent risk factors of lymphatic spread. In our study, 21 patients had lymphatic spread at the time of diagnosis, and only a minority of those had a multicentric cancer. Statistically, nodal metastasis was not found to be associated with multicentricity or bilaterality. However, there was a significant difference in tumor size between the patients with multicentric PTC and the patients with solitary PTC, indicating that the incidence of multicentricity increased with the tumor size. It should be noted here that no cut-off value of tumor size was determined in our study. Lee et al. [10] also reported that bilaterality was found more frequently when the tumor was large. In another study, the presence of three or more tumor foci or bilaterality of tumor tended to be present with larger tumors [11]. In addition to the diameter of tumor, perineural invasion was the other indicator of multicentricity in our study population. Perineural invasion is defined as the presence of tumoral epithelial cells in perineurium, and is usuallly considered a sign of malignancy. Perineural invasion and lymphovascular invasion were reported as an indicator of lymphatic spread and distant meastasis in various cancers such as colon, rectal, and breast cancers [12-15]. Lymphatic metastasis is also one of the leading characteristics of PTC. However, the role of perineural and lymphovascular invasions on the prognosis of PTC has not been clearly defined. In a study from China, multifocal PTC was reported to be more related to vascular invasion than solitary PTC [16]. In our work, perineural invasion, but not lymphovascular invasion, was found to be associated with multicentricity. However, it should be stated here that the number of tumors with perineural invasion was small, which might not allow a powerful statistical assessment to be made. It is well known that multifocal or multicentric PTCs usually have worse outcomes than unifocal PTCs [3, 11]. Therefore, perineural invasion may be a histopathological factor indicating poor prognosis in patients with PTC, especially in those with multicentric cancer.

In contrast to previous studies, other factors such as age, gender, stage of tumor, presence of Hashimato thyroiditis and microcalcification, number of nodules, and extrathyroidal invasion were not found to be associated factors on multicentricity or bilaterality in PTC [16, 17] .

Recurrence is not common in PTC, with an incidence rate of 10-15%. Recurrence is often related to age at diagnosis, diameter of tumor, extrathyroidal extension, lymphatic metastasis, and aggressive histological subtypes [18-21]. Multiplicity is also associated with an increased risk of distant metastasis and regional recurrence [7, 16]. In this cohort of patients, a recurrence rate of 9.2% was observed, but there was no significant association between the recurrence and multicentricity or bilaterality. Although multicentricity is a common feature of PTC, its etiopathogenesis is not yet fully understood. It is also not clear why some PTCs develop multiple tumors arising from metastasis of a single primary carcinoma origin while others have multicentric tumors arising independently from different origins. Both multiplicity and multicentricity may be explained by various genetic factors such as mutations in B-type Raf kinase (BRAF) gene. Today, in most of the medical centers, the detection of BRAF mutation is not a routine tool in the diagnostic work-up of patients with PTC, due to technical, economic, and traditional reasons. This genetic test was also not a part of our study. In fact, BRAF plays a major role in the regulation of cell growth, division, and proliferation, and its mutation is the most common genetic alteration in PTC [22]. It is also seen frequently in the late stages of this cancer. The association between BRAF mutation and worse tumoral features is still controversial [23, 24]. In addition, the BRAF mutation was not significantly associ-

ated with multiple PTC [16].

In conclusion, multicentricity is not an uncommon condition in PTC, and is generally considered to be associated with worse outcomes. Our study showed that tumor size and perineural invasion were the associated factors on multicentricity of PTC. However, large-scale, multicenter clinical and genetic studies are needed to clearly determine the affecting factors on multicentricity of these cancers.

Competing interests

The authors declare that they have no competing interests.

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How to cite this article:
Kılıç MÖ, Bilgiç Cİ, Dener C, İçen D. The Clinicopathological Factors Associated with Multicentricity in Papiller Thyroid Cancer. J Clin Anal Med 2016;7(4): 479-82.